Research Article

Statistics in Medicine

Received XXXX

(www.interscience.wiley.com) DOI: 10.1002/sim.0000

Statistical Consequences of a Successful Lung Allocation System – Recovering Information and Reducing Bias in Models for Urgency

N Tayob*and S. Murray

1. Additional simulation results

We have included a simulation study when covariates affect survival ($\beta_0 = 2.1$, $\beta_1 = -0.125$ and $\beta_2 = 0.1$) and a larger sample size ($n = 400$). These results are comparable to those presented in Table 1 of the main manuscript. The simulated ARE values when comparing our proposed method to the IPCW pseudo observation seem fairly stable for the two sample sizes we simulated (n=300: Mean ARE 2.17; n=400: Mean ARE 2.11). Similarly, comparing our proposed method to the multiple imputation method of Xiang and Murray we see comparable ARE results for the two simulated sample sizes (n=300: Mean ARE 2.16; n=400: Mean ARE 2.11).

Table 1. Comparison of parameter estimates from the IPCW pseudo-observation method (IPCW-PO) and the multiple imputation method (MI), which both use one follow-up window; and estimates using uncensored observations (Uncensored) and our multiple imputation method (MI*), which both use three follow-up windows, with 500 Monte Carlo simulations. M=10 in both multiple imputation methods.

Parameter	IPCW-PO	MI	Uncensored	MI*
		Sample size 400		
$\beta_0 = 2.1$	2.101 [0.001, 0.111, 0.112, 0.936]	2.102 [0.002, 0.110, 0.112, 0.936]	2.070 [-0.030, 0.076, 0.076, 0.938]	2.052 [-0.048, 0.077, 0.078, 0.936]
$\beta_1 = -0.125$	-0.133 [-0.008, 0.145, 0.143, 0.956]	-0.134 [-0.009, 0.145, 0.143, 0.960]	-0.123 [0.002, 0.089, 0.090, 0.958]	-0.119 [0.006, 0.093, 0.092, 0.960]
$\beta_2 = 0.1$	0.109 [0.009, 0.181, 0.177, 0.948]	0.108 [0.008, 0.181, 0.177, 0.948]	0.113 [0.013, 0.133, 0.125, 0.970]	0.105 [0.005, 0.135, 0.129, 0.972]

Empirical Mean
[Bias, Empirical Mean Standard Error,
Empirical Standard Deviation, Coverage of 95% Confidence Interval]

2. Additional example results

We have included the results from the proposed analyses when the one-year follow-up windows are spaced every three months (Table 2) and every one year (Table 3). The parameter estimates for the IPCW pseudo-observation (IPCW-PO)

*Correspondence to: The University of Texas MD Anderson Cancer Center, 1400 Pressler Street, Houston, TX 77030. Tel: (731) 792-8172. Email: ntayob@mdanderson.org.

Copyright © 2014 John Wiley & Sons, Ltd.

method applied to the first follow-up window are invariant to the choice of follow-up windows. The multiple imputation method applied to the first follow-up window is affected by the choice of follow-up windows since the methodology uses parameter estimates from the IPCW pseudo-observation applied to all the follow-up windows. There is minimal change in the parameter estimates from the multiple imputation method applied to the first follow-up window across the different choices of follow-up windows. There is no change in the statistical significant across the different choices of follow-up windows except for CVP in Group B, Creatinine, Sarcoidosis with PA mean$\leq$30mm Hg, PCO_2 and Obliterative Bronchiolitis. The parameter estimates from the multiple imputation method applied to multiple follow up windows are mostly unaffected by the number of follow-up windows except for Continuous Mechanical Ventilation which is not unexpected given our observation of a significant interaction between Continuous Mechanical Ventilation and time. There is no change in the statistical significant across the different choices of follow-up windows except for Creatinine, Diabetes, Obliterative Bronchiolitis, Sarcoidosis with PA mean$\leq$30mm Hg and PCO_2.

Copyright © 2014 John Wiley & Sons, Ltd.

Prepared using simauth.cls

Table 2. Results for urgency model based on the first follow-up window using the IPCW pseudo-observation (IPCW-PO) and the multiple imputation method (MI); and based on 13 follow-up windows every three months using our multiple imputation method (MI*). M=10.

	IPCW-PO			MI			MI*		
	$e^{\hat{\beta}}$	95% CI	p-value	$e^{\hat{\beta}}$	95% CI	p-value	$e^{\hat{\beta}}$	95% CI	p-value
Intercept	663.84	(508.83,866.06)	< 0.0001	560.16	(493.12,636.31)	< 0.0001	579.01	(482.05,695.48)	< 0.0001
Age (per 20 year increase)	0.91	(0.86,0.96)	0.0011	0.92	(0.89,0.95)	< 0.0001	0.93	(0.89,0.97)	0.0035
BMI (per 1 kg/m^2 decrease if BMI$<$20kg/m^2)	0.98	(0.96,0.99)	0.0052	0.98	(0.95,1.00)	0.0420	0.97	(0.96,1.00)	0.0176
Cardiac Index$<$2.0 (ref=CI$\geq$ 2)	0.83	(0.73,0.94)	0.0036	0.90	(0.84,0.96)	0.0028	0.85	(0.77,0.94)	0.0030
CVP in Group B (per 10 mm Hg)	0.79	(0.60,1.02)	0.0709	0.79	(0.68,0.91)	0.0015	0.77	(0.61,0.97)	0.0262
Continuous Mechanical Ventilation (ref=other/no ventilation)	0.17	(0.12,0.24)	< 0.0001	0.29	(0.23,0.37)	< 0.0001	0.14	(0.11,0.17)	< 0.0001
Creatinine (Age$>$ 18 years)	0.94	(0.86,1.02)	0.1264	0.96	(0.92,1.00)	0.0487	0.96	(0.89,1.03)	0.1998
Diabetes (ref=no diabetes)	0.93	(0.86,1.00)	0.0514	0.95	(0.91,0.98)	0.0019	0.96	(0.91,1.00)	0.0575
Diagnosis group (ref=group A)									
Group B	1.05	(0.79,1.39)	0.7567	1.02	(0.87,1.20)	0.8145	1.11	(0.86,1.44)	0.3889
Group C	0.82	(0.71,0.96)	0.0126	0.89	(0.81,0.96)	0.0075	0.86	(0.76,0.97)	0.0207
Group D	1.09	(0.94,1.26)	0.2611	1.03	(0.94,1.12)	0.4947	1.06	(0.93,1.19)	0.3554
Bronchiectasis	0.93	(0.82,1.05)	0.2371	0.97	(0.91,1.03)	0.3141	0.94	(0.83,1.07)	0.3059
Eisenmenger Syndrome	1.39	(1.08,1.78)	0.0105	1.08	(0.86,1.34)	0.5111	1.21	(0.97,1.52)	0.0828
Lymphangioleiomyomatosis	1.00	(0.83,1.20)	0.9618	1.05	(0.97,1.13)	0.2028	1.02	(0.85,1.22)	0.8164
Obliterative Bronchiolitis	1.25	(1.00,1.56)	0.0515	1.10	(0.98,1.24)	0.1100	1.23	(1.03,1.47)	0.0271
Pulmonary Fibrosis Other	0.91	(0.78,1.06)	0.2315	1.02	(0.96,1.08)	0.5120	1.00	(0.92,1.09)	0.9674
Sarcoidosis with PA mean$>$30mm Hg	1.19	(0.95,1.49)	0.1273	1.23	(1.13,1.33)	< 0.0001	1.26	(1.03,1.47)	0.0005
Sarcoidosis with PA mean$\leq$30mm Hg	0.93	(0.83,1.05)	0.2511	0.91	(0.84,0.98)	0.0109	0.93	(0.84,1.03)	0.1455
FVC (per 10% decrease if FVC %predicted$<$80%) in Group D	0.94	(0.91,0.96)	< 0.0001	0.96	(0.95,0.98)	0.0001	0.95	(0.93,0.97)	0.0001
No assistance with ADL (ref=some/total assisstance)	1.02	(0.97,1.07)	0.3791	0.98	(0.96,1.01)	0.1946	0.99	(0.95,1.03)	0.5756
O_2 requirement at rest in Group B	0.94	(0.90,0.98)	0.0022	0.95	(0.93,0.98)	0.0005	0.92	(0.89,0.97)	0.0009
O_2 requirement at rest in Groups A, C or D	0.92	(0.91,0.93)	< 0.0001	0.93	(0.93,0.94)	< 0.0001	0.92	(0.91,0.92)	< 0.0001
PCO_2 (per 10mm Hg)	0.96	(0.92,0.99)	0.0252	0.98	(0.96,1.00)	0.0216	0.98	(0.95,1.00)	0.1512
PCO_2 increase of $\geq 15\%$ (PCO_2 increase of $< 15\%$)	0.97	(0.65,1.44)	0.8857	1.02	(0.96,1.09)	0.5266	0.87	(0.65,1.17)	0.3511
PA systolic in Group A (per 10 mm Hg increase if PA systolic$>$ 40mm Hg)	0.99	(0.94,1.04)	0.6038	0.98	(0.95,1.01)	0.1147	0.98	(0.94,1.03)	0.4313
PA systolic in Group B, C or D (per 10 mm Hg increase)	0.97	(0.94,0.99)	0.0129	0.97	(0.96,0.99)	0.0006	0.96	(0.94,0.98)	0.0025
Six-min walk distance (per 1000 feet)	1.22	(1.13,1.32)	< 0.0001	1.13	(1.09,1.17)	< 0.0001	1.15	(1.09,1.21)	< 0.0001

Effect size, $e^{\hat{\beta}}$, per unit increase in the continuous risk factor unless otherwise stated; Effect size for reference categories of categorical risk factors is 1.
Body Mass Index (BMI); Cardiac Index (CI); Central Venous Pressure (CVP); Activities of Daily Living (ADL); Pulmonary Artery (PA)

Copyright © 2014 John Wiley & Sons, Ltd.

Table 3. Results for urgency model based on the first follow-up window using the IPCW pseudo-observation (IPCW-PO) and the multiple imputation method (MI); and based on four follow-up windows every twelve months using our multiple imputation method (MI*). M=10.

	IPCW-PO			MI			MI*		
	$e^{\hat{\beta}}$	95% CI	p-value	$e^{\hat{\beta}}$	95% CI	p-value	$e^{\hat{\beta}}$	95% CI	p-value
Intercept	663.84	(508.83,866.06)	< 0.0001	579.21	(480.09,698.81)	< 0.0001	592.63	(477.52,735.49)	< 0.0001
Age (per 20 year increase)	0.91	(0.86,0.96)	0.0011	0.93	(0.89,0.97)	0.0017	0.93	(0.89,0.98)	0.0077
BMI (per 1 kg/m^2 decrease if BMI$<$20kg/m^2)	0.98	(0.96,0.99)	0.0052	0.98	(0.96,1.00)	0.0383	0.98	(0.95,1.00)	0.0387
Cardiac Index$<$2.0 (ref=CI$\geq$ 2)	0.83	(0.73,0.94)	0.0036	0.88	(0.80,0.97)	0.0104	0.85	(0.77,0.95)	0.0068
CVP in Group B (per 10 mm Hg)	0.79	(0.60,1.02)	0.0709	0.75	(0.63,0.90)	0.0031	0.78	(0.62,0.97)	0.0296
Continuous Mechanical Ventilation (ref=other/no ventilation)	0.17	(0.12,0.24)	< 0.0001	0.19	(0.15,0.24)	< 0.0001	0.14	(0.11,0.18)	< 0.0001
Creatinine (Age$>$ 18 years)	0.94	(0.86,1.02)	0.1264	0.93	(0.88,0.99)	0.0329	0.94	(0.88,1.01)	0.0672
Diabetes (ref=no diabetes)	0.93	(0.86,1.00)	0.0514	0.95	(0.91,0.99)	0.0192	0.95	(0.91,1.00)	0.0547
Diagnosis group (ref=group A)									
Group B	1.05	(0.79,1.39)	0.7567	1.14	(0.93,1.41)	0.2004	1.12	(0.91,1.43)	0.3350
Group C	0.82	(0.71,0.96)	0.0126	0.90	(0.81,0.99)	0.0321	0.87	(0.78,0.98)	0.0226
Group D	1.09	(0.94,1.26)	0.2611	1.07	(0.96,1.19)	0.2194	1.08	(0.95,1.22)	0.2337
Bronchiectasis	0.93	(0.82,1.05)	0.2371	0.97	(0.88,1.06)	0.4536	0.94	(0.83,1.06)	0.2939
Eisenmenger Syndrome	1.39	(1.08,1.78)	0.0105	1.19	(0.99,1.43)	0.0655	1.23	(0.98,1.54)	0.0714
Lymphangioleiomyomatosis	1.00	(0.83,1.20)	0.9618	1.05	(0.92,1.20)	0.4350	1.02	(0.85,1.22)	0.8649
Obliterative Bronchiolitis	1.25	(1.00,1.56)	0.0515	1.18	(1.01,1.38)	0.0352	1.23	(1.02,1.47)	0.0313
Pulmonary Fibrosis Other	0.91	(0.78,1.06)	0.2315	1.00	(0.93,1.09)	0.9033	0.99	(0.91,1.08)	0.7454
Sarcoidosis with PA mean$>$30mm Hg	1.19	(0.95,1.49)	0.1273	1.29	(1.17,1.43)	0.0001	1.26	(1.12,1.43)	0.0010
Sarcoidosis with PA mean$\leq$30mm Hg	0.93	(0.83,1.05)	0.2511	0.93	(0.84,1.03)	0.1613	0.94	(0.83,1.06)	0.2907
FVC (per 10% decrease if FVC %predicted$<$80%) in Group D	0.94	(0.91,0.96)	< 0.0001	0.96	(0.94,0.98)	0.0011	0.95	(0.93,0.97)	0.0007
No assistance with ADL (ref=some/total assisstance)	1.02	(0.97,1.07)	0.3791	0.98	(0.95,1.02)	0.2892	0.99	(0.95,1.03)	0.5246
O_2 requirement at rest in Group B	0.94	(0.90,0.98)	0.0022	0.93	(0.89,0.97)	0.0006	0.92	(0.88,0.96)	0.0009
O_2 requirement at rest in Groups A, C or D	0.92	(0.91,0.93)	< 0.0001	0.92	(0.91,0.93)	< 0.0001	0.92	(0.91,0.92)	< 0.0001
PCO_2 (per 10mm Hg)	0.96	(0.92,0.99)	0.0252	0.98	(0.95,1.00)	0.0547	0.98	(0.95,1.00)	0.0928
PCO_2 increase of $\geq 15\%$ (PCO_2 increase of $< 15\%$)	0.97	(0.65,1.44)	0.8857	1.01	(0.87,1.17)	0.8908	0.93	(0.62,1.39)	0.6983
PA systolic in Group A (per 10 mm Hg increase if PA systolic$>$ 40mm Hg)	0.99	(0.94,1.04)	0.6038	0.98	(0.95,1.02)	0.3662	0.98	(0.94,1.03)	0.4434
PA systolic in Group B, C or D (per 10 mm Hg increase)	0.97	(0.94,0.99)	0.0129	0.96	(0.95,0.98)	0.0001	0.96	(0.94,0.98)	0.0004
Six-min walk distance (per 1000 feet)	1.22	(1.13,1.32)	< 0.0001	1.15	(1.09,1.20)	< 0.0001	1.15	(1.08,1.21)	0.0002

Effect size, $e^{\hat{\beta}}$, per unit increase in the continuous risk factor unless otherwise stated; Effect size for reference categories of categorical risk factors is 1.
Body Mass Index (BMI); Cardiac Index (CI); Central Venous Pressure (CVP); Activities of Daily Living (ADL); Pulmonary Artery (PA)

Copyright © 2014 John Wiley & Sons, Ltd.